

10/549804**JC05 Rec'd PCT/PTO 19 SEP 2005****LISTING OF CLAIMS**

1. *(currently amended)*: A method for making obtaining a prognosis of enhanced or reduced recovery from an inflammatory condition in for a patient subject having, or at risk of developing, the an-inflammatory condition, the method comprising:

determining a genotype defined by for one or more polymorphic polymorphism sites in the plasminogen-activator-inhibitor-1 (PAI-1) gene in for the patient subject, wherein said genotype is predictive or indicative of an enhanced or reduced ability of the patient subject to recover from the [[an]] inflammatory condition compared to a subject not having the genotype, with the proviso provided that the one or more polymorphic polymorphism sites is not a single polymorphism solely at a polymorphism at a site corresponding to nucleotide position 837 of SEQ ID NO:1.

2. *(currently amended)*: The method of claim 1, wherein the one or more polymorphic polymorphism sites includes position 12580 of SEQ ID NO:1 or a polymorphic polymorphism site in total linkage disequilibrium thereto.

3. *(currently amended)* The method of claim 2, wherein the one or more polymorphic polymorphism sites is are selected from the group consisting of positions 5645, 7121, 7437, 8070, 8406, 9463, 9466, 12219, 12580, 13889 and 14440 of SEQ ID NO:1.

4. *(currently amended)* The method of claim 1, wherein the genotype is defined by comprises a combination of two or more polymorphic polymorphism sites, the combination being a grouping selected from the group of the following nucleotides positions correspond to of SEQ ID NO:1:

- (A) 664 A and 2037 T;
- (B) 664 A and 2362 [[-]] deletion;
- (C) 664 A and 2852 A;
- (D) 664 A and 5834 A;
- (E) 837 [[-]] deletion and 2037 T;
- (F) 837 [[-]] deletion and 2362 [[-]] deletion;
- (G) 837 [[-]] deletion and 2852 A;
- (H) 837 [[-]] deletion and 5834 A;

- (I) a combination of three of the following polymorphic nucleotides:
- (i) one of 5878 G, 7343 G and 13605 A,
 - (ii) one of 7365 T, 7729 insertion, 7771 A and 12750 A; and
 - (iii) one of 4588 T, 5404 G, 5686 A, 5984 A, and 11312 A; or
- (J) a combination of four of the following polymorphic nucleotides selected as shown below:
- (i) one combination of two nucleotides 2846 A/10381 T, 6821 T/10381 T and 9759 G/10381 T
 - (ii) one of 7365 T, 7729 insertion, 7771 A and 12750 A; and
 - (iii) one of 4588 T, 5404 G, 5686 A, 5984 A, and 11312 A;

one of	5878 G and one of	7365 T	and one of	4588 T	
	7343 G	7729 +		5404 G	
	13605 A	7771 A		5686 A	
		12750 A		5984 A	
				11312 A; and	
one of	2846 A and 10381 T	and one of	7365 T	and one of	4588 T
	6821 T and 10381 T		7729 +		5404 G
	9759 G and 10381 T		7771 A		5686 A
			12750 A		5984 A
					11312 A.

5. *(currently amended)* The method of claim 1 ~~any one of claims 1-4~~, further comprising comparing the determined genotype ~~so determined~~ with ~~known genotypes which are known to be~~ indicative of, ~~or associated with~~, a prognosis of ~~for~~ recovery from (i) ~~the same~~ inflammatory condition with which ~~as for the patient subject is affected~~ or (ii) another inflammatory condition.

6. *(currently amended)* The method of claim 1 ~~any one of claims 1-5~~, further comprising ascertaining ~~obtaining~~ a PAI-1 ~~plasminogen activator inhibitor 1~~ gene sequence of the patient subject.

7. *(currently amended)* The method of claim 1 ~~any one of claims 1-5~~, wherein said the genotype determination ~~determining of genotype~~ is performed on a nucleic acid sample from the patient subject.

8. *(currently amended)* The method of claim 7, further comprising the step of obtaining the nucleic acid sample from the ~~patient~~ subject.

9. *(currently amended)* The method of claim 7 ~~any one of claims 1-8~~, wherein said the genotype determination ~~determining of genotype~~ employs ~~comprises~~ one or more of the following methods:

- (a) restriction fragment length analysis;
- (b) sequencing;

- (c) hybridization;
- (d) oligonucleotide ligation assay;
- (e) ligation rolling circle amplification;
- (f) 5' nuclease assay;
- (g) a polymerase proofreading methods;
- (h) allele specific PCR; and
- (i) reading sequence data.

10. *(currently amended)*: The method of claim 1 ~~any one of claims 1-9~~, wherein the genotype of the subject patient is predictive or indicative of a decreased likelihood of recovery from ~~[[an]]~~ the inflammatory condition.

11. *(currently amended)*: The method of claim 10, wherein the subject is critically ill and the prognosis is ~~indicative~~ one of severe cardiovascular or respiratory dysfunction ~~in critically ill patients~~.

12. *(currently amended)*: The method of claim 10 ~~or 11~~, wherein the genotype is selected from ~~the group of single~~ nucleotide polymorphic polymorphism sites and combined polymorphic polymorphism sites at the following nucleotide positions of SEQ ID NO:1:

- (A) 5645 T;
- (B) 7121 G;
- (C) 7437 T;
- (D) 8070 A;
- (E) 8406 C;
- (F) 9463 G;
- (G) 9466 T;
- (H) 12219 C;
- (I) 12580 G;
- (J) 13889 C;
- (K) 14440 A;
- (L) 664 A and 2037 T;
- (M) 664 A and 2362 ~~[[-]]~~ deletion;
- (N) 664 A and 2852 A;
- (O) 664 A and 5834 A;
- (P) 837 ~~[[-]]~~ deletion and 2037 T;

- (Q) 837 ~~[[-]]~~ deletion and 2362 ~~[[-]]~~ deletion;
- (R) 837 ~~[[-]]~~ deletion and 2852 A; and
- (S) 837 ~~[[-]]~~ deletion and 5834 A.

13. *(currently amended)*: The method of claim 1 ~~any one of claims 1-9~~, wherein the genotype of the subject patient is predicative or indicative of an increased likelihood of recovery from ~~[[an]]~~ the inflammatory condition.

14. *(currently amended)*: The method of claim 13, wherein the subject is critically ill and the prognosis is ~~indicative one~~ of less severe cardiovascular or respiratory dysfunction ~~in a critically ill patients~~.

15. *(currently amended)*: The method of claim 13 ~~or 14~~, wherein the genotype is selected from the ~~group of~~ single polymorphic polymorphism sites and combined polymorphic polymorphism sites ~~consisting of~~ at the following nucleotide positions of SEQ ID NO:1:

- (A) 5645 C;
- (B) 7121 A;
- (C) 7437 C;
- (D) 8070 G;
- (E) 8406 T;
- (F) 9463 A;
- (G) 9466 C;
- (H) 12219 T;
- (I) 12580 T;
- (J) 13889 T;
- (K) 14440 G;

(L) a combination of three of the following polymorphic nucleotides:

- (i) one of 5878 G, 7343 G and 13605 A,
- (ii) one of 7365 T, 7729 insertion, 7771 A and 12750 A; and
- (iii) one of 4588 T, 5404 G, 5686 A, 5984 A, and 11312 A; or

(M) a combination of three of the following polymorphic nucleotides or pairs of polymorphic nucleotides:

- (i) one of 2846 A/10381 T, 6821 T/10381 T and 9759 G
- (ii) one of 7365 T, 7729 insertion, 7771 A and 12750 A; and
- (iii) one of 4588 T, 5404 G, 5686 A, 5984 A, and 11312 A.

one of 5878 G and one of 7365 T and one of 4588 T		
7343 G	7729 +	5404 G
13605 A	7771 A	5686 A
	12750 A	5984 A
		11312 A; and
one of 2846 A and 10381 T and one of 7365 T and one of 4588 T		
6821 T	7729 +	5404 G
9759 G	7771 A	5686 A
	12750 A	5984 A
		11312 A.

16. *(currently amended)*: The method of claim 1 ~~any one of claims 1-15~~, wherein the inflammatory condition is one that is due to, or associated with, selected from the group consisting of: sepsis, septicemia, fever, a bacterial viral, fungal or parasitic infection, a medical or surgical condition associated with increased risk of infection or sepsis, pneumonia, septic shock, systemic inflammatory response syndrome (SIRS), Acute Respiratory Distress Syndrome (ARDS), acute lung injury, infection, pancreatitis, bacteremia, peritonitis, abdominal abscess, inflammation due to trauma, inflammation due to surgery, chronic inflammatory disease, ischemia, ischemia-reperfusion injury of an organ or tissue, tissue damage due to (i) disease, tissue damage due to (ii) chemotherapy or (iii) radiotherapy, or and a reactions to an ingested, inhaled, infused, injected, or delivered substances, glomerulonephritis, bowel infection, opportunistic infections, and for patients undergoing major surgery or kidney failure and dialysis, immunosuppressive therapy, patients who are immunocompromised, patients on immunosuppressive agents, patients with HIV/AIDS, patients with suspected endocarditis, patients with fever, patients with fever of unknown origin, patients with cystic fibrosis, patients with diabetes mellitus, patients with chronic renal failure, patients with bronchiectasis, patients with chronic obstructive lung pulmonary disease (COPD), chronic bronchitis, emphysema, or asthma, patients with febrile neutropenia, patients with meningitis, patients with septic arthritis, patients with urinary tract infection, patients with necrotizing fasciitis, patients with other suspected Group A streptococcus infection, patients who have had a splenectomy, patients with recurrent or suspected enterococcus infection, other medical and surgical conditions associated with increased risk of infection, Gram positive sepsis, Gram negative sepsis, culture negative sepsis, fungal sepsis, meningococemia, post-pump syndrome, cardiac stun syndrome, myocardial infarction, stroke, congestive heart failure, hepatitis, cirrhosis, epiglottitis, E. coli 0157:H7, malaria, gas gangrene, toxic shock syndrome, mycobacterial tuberculosis, Pneumocystis carinii, pneumonia, Leishmaniasis, hemolytic uremic syndrome/thrombotic thrombocytopenic purpura, Dengue hemorrhagic fever, pelvic inflammatory disease, Legionella, Lyme disease, Influenza A, Epstein Barr virus, encephalitis, inflammatory diseases and

autoimmunity including rheumatoid arthritis, osteoarthritis, systemic lupus erythematosus, inflammatory bowel disease, idiopathic pulmonary fibrosis, sarcoidosis, hypersensitivity pneumonitis, systemic vasculitis, Wegener's granulomatosis; an organ or tissue transplants and/or transplant rejection including heart, liver, lung kidney bone marrow, graft-versus-host disease, transplant rejection, sickle cell anemia, nephrotic syndrome, or toxicity caused by a therapy with a monoclonal antibody or of agents such as OKT3 cytokine therapy, and cirrhosis.

17. *(currently amended)*: The method of claim 16 ~~any one of claims 1-16~~, wherein the inflammatory condition is SIRS ~~systemic inflammatory response syndrome~~.

18. *(currently amended)*: A method of identifying a polymorphism in a PAI-1 gene sequence that correlates with or is associated with a patient prognosis of recovery from an inflammatory condition in a subject, the method comprising:

- (a) obtaining PAI-1 gene sequence information from a plurality group of subjects ~~patients~~;
- (b) based on the sequence information of (a), identifying at least one site of at least one polymorphism in the PAI-1 gene;
- (c) determining genotypes defined by said at least one polymorphism at the site ~~for individual subjects patients in the group~~;
- (d) determining recovery an ability of individual subjects patients in the group to recover from the inflammatory condition; and
- (e) correlating the genotypes determined in at step (c) with the subjects' recovery patient abilities determined in at step (d),

thereby identifying said polymorphism in said PAI-1 gene.

19. *(currently amended)*: The method of claim 18 wherein the inflammatory condition is one that is due to, or associated with, selected from the group consisting of: sepsis, septicemia, fever, a bacterial viral, fungal or parasitic infection, a medical or surgical condition associated with increased risk of infection or sepsis, pneumonia, septic shock, systemic inflammatory response syndrome (SIRS[[]]), Acute Respiratory Distress Syndrome (ARDS[[]]), acute lung injury, infection, pancreatitis, bacteremia, peritonitis, abdominal abscess, inflammation due to trauma, inflammation due to surgery, chronic inflammatory disease, ischemia, ischemia-reperfusion injury of an organ or tissue, tissue damage due to (i) disease, tissue damage due to (ii) chemotherapy or (iii) radiotherapy, or and a reactions to an ingested, inhaled, infused, injected, or delivered substances, glomerulonephritis, bowel infection, opportunistic infections, and for

~~patients undergoing major surgery or kidney failure and dialysis, immunosuppressive therapy, patients who are immunocompromised, patients on immunosuppressive agents, patients with HIV/AIDS, patients with suspected endocarditis, patients with fever, patients with fever of unknown origin, patients with cystic fibrosis, patients with diabetes mellitus, patients with chronic renal failure, patients with bronchiectasis, patients with chronic obstructive lung disease (COPD), chronic bronchitis, emphysema, or asthma, patients with febrile neutropenia, patients with meningitis, patients with septic arthritis, patients with urinary tract infection, patients with necrotizing fasciitis, patients with other suspected Group A streptococcus infection, patients who have had a splenectomy, patients with recurrent or suspected enterococcus infection, other medical and surgical conditions associated with increased risk of infection, Gram positive sepsis, Gram negative sepsis, culture negative sepsis, fungal sepsis, meningococemia, post-pump syndrome, cardiac stun syndrome, myocardial infarction, stroke, congestive heart failure, hepatitis, cirrhosis, epiglottitis, E. coli 0157:H7, malaria, gas gangrene, toxic shock syndrome, mycobacterial tuberculosis, *Pneumocystis carinii*, pneumonia, Leishmaniasis, hemolytic uremic syndrome/thrombotic thrombocytopenic purpura, Dengue hemorrhagic fever, pelvic inflammatory disease, Legionella, Lyme disease, Influenza A, Epstein Barr virus, encephalitis, inflammatory diseases and autoimmunity including rheumatoid arthritis, osteoarthritis, systemic lupus erythematosus, inflammatory bowel disease, idiopathic pulmonary fibrosis, sarcoidosis, hypersensitivity pneumonitis, systemic vasculitis, Wegener's granulomatosis; an organ or tissue transplants and/or transplant rejection including heart, liver, lung kidney bone marrow, graft-versus-host disease, transplant rejection, sickle cell anemia, nephrotic syndrome, or toxicity caused by a therapy with a monoclonal antibody or a f-agents such as OKT3 cytokine therapy, and cirrhosis.~~

20. (currently amended): A kit useful for determining a genotype of a subject or subjects at a defined polymorphic nucleotide position at within a polymorphism site in a PAI-1 gene sequence from the subject or subjects a patient to which genotype is associated with provide a prognosis of the subject's patient's ability to recover from an inflammatory condition, the kit comprising, in a package:

- (a) a restriction enzyme with specificity that distinguishes ~~capable of distinguishing~~ alternate nucleotides at the polymorphic polymorphism site or sites; or
- (b) a labeled oligonucleotide having sufficient complementarity nucleotides to an sequence that is contiguous with adjacent sequence at or near the polymorphic polymorphism site such that the oligonucleotide hybridizes in a distinguishable

manner to a sequence that comprises and capable of distinguishing said an
alternate nucleotide or nucleotides at the polymorphic site or sites,
with the proviso provided that the polymorphism site is not solely a polymorphism at a site
corresponding to position 837 of SEQ ID NO:1.

21. *(currently amended)*: The kit of claim 20, wherein the polymorphic polymorphism site is at ~~corresponds to~~ one or more of nucleotide positions 5645, 7121, 7437, 8070, 8406, 9463, 9466, 12219, 12580, 13889 and 14440 of SEQ ID NO:1.

22. *(currently amended)*: The kit of claim 21, where the polymorphic polymorphism site is corresponds to nucleotide position 12580 of SEQ ID NO:1.

23. *(currently amended)*: The kit of claim 20, ~~21 or 22~~ comprising said restriction enzyme and an oligonucleotide primer or a set of oligonucleotides suitable to amplify a region flanking surrounding the polymorphic polymorphism site.

24. *(currently amended)*: The kit of claim 23, further comprising a polymerization agent that promotes or permits nucleotide polymerization.

25. *(currently amended)*: The kit of ~~any one of claims~~ claim 20[[~~-24~~]], further comprising instructions for using the kit to determine genotype.

26. *(currently amended)*: A method for identifying ~~selecting a group of~~ subjects patients as being suitable for a trial that tests ~~determining the~~ efficacy of a candidate drug known to be, or suspected of being, useful for the treatment of an inflammatory disease or condition, the method comprising

(a) determining a genotype defined by ~~for~~ one or more polymorphic polymorphism sites in the PAI-1 plasminogen activator inhibitor-1 gene for each subject patient, wherein said genotype is indicative of the subject's patient's recovery ability to ~~recover~~ from the inflammatory condition; and

(b) sorting subjects patients into a suitable or unsuitable group for said trial based on their subjects' genotype,

with the proviso provided that the polymorphic polymorphism site is not solely a polymorphism
at a site corresponding to position 837 of SEQ ID NO:1.

27. *(currently amended)*: ~~The method of claim 26 further comprising, comparing patient response to the candidate drug based on genotype of the patient~~ A method for testing a candidate drug for its efficacy in the treatment of an inflammatory disease or condition wherein said disease or condition is associated with a genotype defined by a polymorphism in a PAI-1 gene, comprising:

- (a) identifying subjects that are suitable for a trial that tests said candidate drug in accordance with claim 26; and
- (b) administering said candidate drug to each of said subjects, and comparing the subjects' responses to said candidate drug in comparison with the subjects' genotype,

thereby testing said candidate drug.

28. *(currently amended)*: The method of claim 27, wherein a subject's ~~patient~~ response to said candidate drug is measured ~~determined by each patient's~~ as the ability to recover from the inflammatory condition.